Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides (from the ANCHOR Study)

Christie M. Ballantyne, MD[a,*], Harold E. Bays, MD[b], John J. Kastelein, MD, PhD[c], Evan Stein, MD, PhD[d], Jonathan L. Isaacsohn, MD[d], Rene A. Braeckman, PhD[e], and Paresh N. Soni, MD, PhD[e]

AMR101 is an ω-3 fatty acid agent containing ≥96% pure icosapent-ethyl, the ethyl ester of eicosapentaenoic acid. The efficacy and safety of AMR101 were evaluated in this phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial (ANCHOR) in high-risk statin-treated patients with residually high triglyceride (TG) levels (≥200 and <500 mg/dl) despite low-density lipoprotein (LDL) cholesterol control (≥40 and <100 mg/dl). Patients (n = 702) on a stable diet were randomized to AMR101 4 or 2 g/day or placebo. The primary end point was median percent change in TG levels from baseline versus placebo at 12 weeks. AMR101 4 and 2 g/day significantly decreased TG levels by 21.5% (p <0.0001) and 10.1% (p = 0.0005), respectively, and non-high-density lipoprotein (non-HDL) cholesterol by 13.6% (p <0.0001) and 5.5% (p = 0.0054), respectively. AMR101 4 g/day produced greater TG and non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. AMR101 4 g/day decreased LDL cholesterol by 6.2% (p = 0.0067) and decreased apolipoprotein B (9.3%), total cholesterol (12.0%), very-low-density lipoprotein cholesterol (24.4%), lipoprotein-associated phospholipase A_2 (19.0%), and high-sensitivity C-reactive protein (22.0%) versus placebo (p <0.001 for all comparisons). AMR101 was generally well tolerated, with safety profiles similar to placebo. In conclusion, AMR101 4 g/day significantly decreased median placebo-adjusted TG, non-HDL cholesterol, LDL cholesterol, apolipoprotein B, total cholesterol, very-low-density lipoprotein cholesterol, lipoprotein-associated phospholipase A_2, and high-sensitivity C-reactive protein in statin-treated patients with residual TG elevations. **(Am J Cardiol 2012;110:984–992)**

In association with an increasing prevalence of obesity and diabetes in recent decades, the number of patients with elevated serum triglycerides (TGs) has markedly increased.[1] In patients with fasting TG levels ≥200 and <500 mg/dl, low-density lipoprotein (LDL) cholesterol is the primary lipid target, with statins being first-line therapy for preventing atherosclerotic coronary heart disease.[2] If TG levels remain ≥200 and <500 mg/dl after optimization of LDL

[a]Baylor College of Medicine and the Methodist DeBakey Heart and Vascular Center, Houston, Texas; [b]Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky; [c]Academic Medical Center, Amsterdam, The Netherlands; [d]Medpace, Cincinnati, Ohio; [e]Amarin Pharma, Inc., Bedminster, New Jersey. Manuscript received March 2, 2012; revised manuscript received and accepted May 23, 2012.

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*Corresponding author: Tel: 713-798-4951; fax: 713-798-3057.

E-mail address: cmb@bcm.tmc.edu (C.M. Ballantyne).

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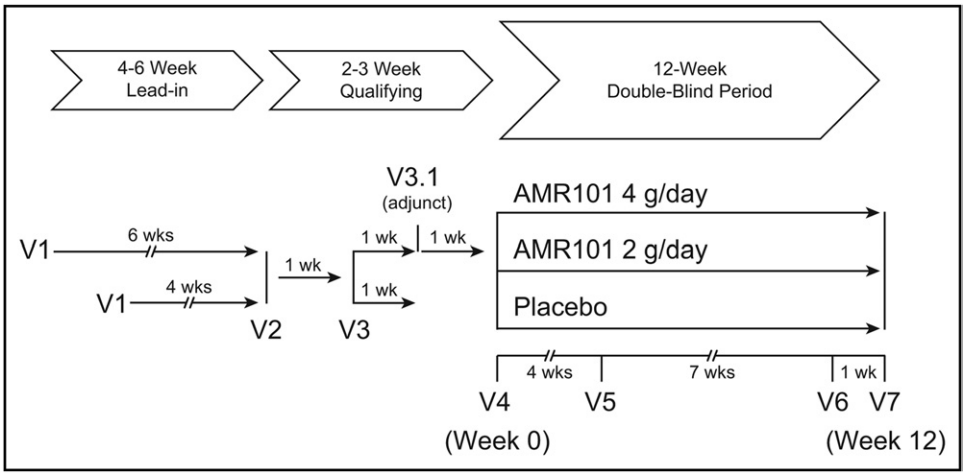

Figure 1. Study design. The screening period consisted of a 4- to 6-week lead-in period during which patients underwent diet and lifestyle stabilization and nonstatin lipid-altering treatment washout if necessary. At the first screening visit, patients not taking a statin were initiated on statin therapy and likely to achieve a low-density lipoprotein cholesterol goal of <100 mg/dl and all patients received counseling on the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.[2] Patients then entered a 2- to 3-week qualifying period. Lipid qualifications included an average fasting triglyceride level ≥200 and <500 mg/dl and an average fasting low-density lipoprotein cholesterol level ≥40 and <100 mg/dl based on the average (arithmetic mean) of 2 visits. If the average triglyceride and/or low-density lipoprotein cholesterol level was outside the required range, an additional measurement could be obtained at a third visit 1 week later, with eligibility determined based on the last 2 visits. Eligible patients were randomized 1 week later to AMR101 4 g/day (2 AMR101 1-g capsules 2 times/day), AMR101 2 g/day (1 AMR101 1-g capsule plus 1 matching placebo capsule 2 times/day), or placebo (2 matching placebo capsules 2 times/day). Investigators and patients were blinded to treatment assignment throughout the double-blinded, placebo-controlled, 12-week treatment period. Visit 1 (V1) was 6 weeks for patients requiring washout and 4 weeks for patients not requiring washout. V2 to V7 = visits 2 to 7.

cholesterol levels with statin therapy, adjunctive treatment options include lifestyle interventions, fibrates, niacin, ezetimibe, and ω-3 fatty acids.[3] AMR101 is an ω-3 fatty acid investigational new drug containing ≥96% pure icosapent-ethyl (the ethyl ester of eicosapentaenoic acid [EPA]; United States Adopted Name [generic] and International Nonproprietary Name). This study (ANCHOR) assessed the efficacy and safety of AMR101 in statin-treated patients at high cardiovascular risk with well-controlled LDL cholesterol and residually high TG levels (≥200 and <500 mg/dl).

Methods

The ANCHOR study was a phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial conducted at 97 sites in the United States from December 2009 through February 2011. The protocol was approved by the appropriate institutional review boards, and all patients underwent the informed consent process before enrollment, as evidenced by their written informed consent. The clinical trial registration number was NCT01047501 (available at: *http://clinicaltrials.gov/ct2/show/NCT01047501*).

The study design is explained in Figure 1. Inclusion criteria included patients >18 years of age and at high risk for cardiovascular disease as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines[2] who were willing to maintain stable diet and exercise throughout the study; at the first TG-qualifying visit, patients were required to have been on ≥4 weeks of stable statin therapy (atorvastatin, rosuvastatin, or simvastatin; with or without ezetimibe) at doses likely to achieve "optimal" LDL cholesterol for high-risk patients (≥40 and <100 mg/dl) and continue such treatment throughout the study. To facilitate enrollment, a protocol amendment was implemented after approximately 1/2 of patients were randomized: the hemoglobin A1c exclusion criterion was increased from 9.0% to >9.5%; based on known within-patient variability for TG and LDL cholesterol, entry criteria were expanded so the mean of the 2 TG-qualifying values was ≥185 mg/dl with ≥1 of the 2 values ≥200 mg/dl; and the upper limit of the LDL cholesterol entry criteria was increased by 15% to ≤115 mg/dl.

Exclusion criteria included body mass index >45 kg/m^2, a weight change >3 kg from the first visit to the end of the qualifying period, non-high-density lipoprotein (non-HDL) cholesterol levels <100 mg/dl, known nephrotic range (>3 g/day) proteinuria, malignancy, bariatric surgery, long-term treatment with antihypertensive and antidiabetic medications, treatment with weight-loss drugs, thyroid-stimulating hormone >1.5 times upper limit of normal, alanine aminotransferase or aspartate aminotransferase >3 times upper limit of normal, and unexplained creatine kinase concentration >3 times upper limit of normal or creatine kinase increase from known muscle disease.

The primary end point was median placebo-adjusted percent change in TG levels from baseline to week 12 (study end). Baseline TG level was calculated as the average of levels at randomization and 1 week previously. TG value at study end was calculated as the average of weeks 11 and 12. Prespecified secondary efficacy end points included median placebo-adjusted percent change in non-HDL cholesterol, LDL cholesterol, apolipoprotein B, very-low-density lipoprotein (VLDL), and lipoprotein-associated phospholipase A_2. Exploratory end points included median placebo-adjusted percent change in total cholesterol, HDL

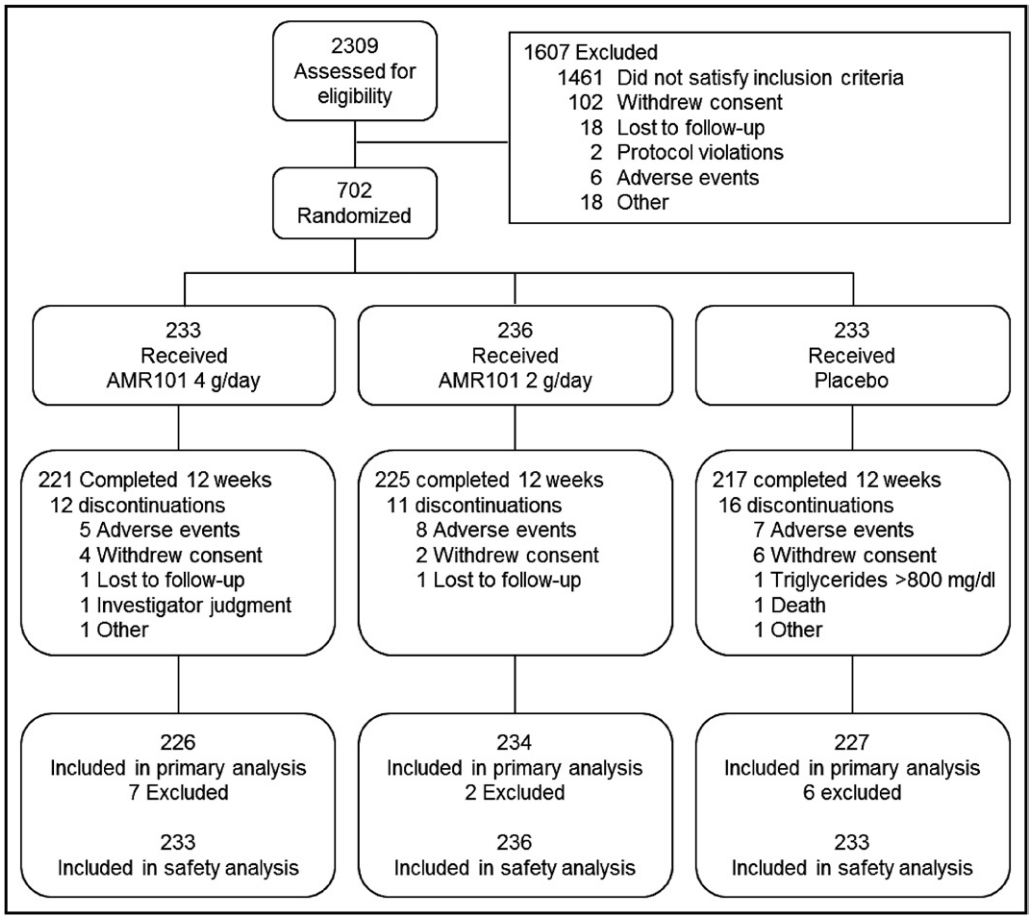

Figure 2. Patient disposition.

cholesterol, VLDL-TG, and high-sensitivity C-reactive protein. Safety assessments, blood and urine tests, and efficacy end-point assessments were analyzed as previously described; high-sensitivity C-reactive protein was measured with the same assay as previously described for lipoprotein-associated phospholipase A_2.[4]

A sample size of 194 completed patients per treatment arm was required to provide 90.6% power to detect a difference of 15% between AMR101 4 g/day and placebo in percent change from baseline in fasting TG levels, assuming an SD of 45% in TG measurements and a significance level (p value) <0.05, and 80% power to demonstrate noninferiority ($p < 0.025$, 1-sided) of the LDL cholesterol response between AMR101 4 g/day and placebo with a +6% margin. To accommodate a 10% drop-out rate, recruitment was planned for 648 randomized patients.

All efficacy analyses were performed on the intent-to-treat population (randomized patients who received ≥ 1 dose of study drug and had baseline and ≥ 1 postrandomization efficacy measurements) using an analysis of covariance model with treatment, type of statin, gender, and presence of diabetes as factors and baseline TG as a covariate. If no significant departure from normality was observed, parametric testing was planned for each comparison between AMR101 and placebo. For each efficacy end point, if a significant departure from normality was observed ($p < 0.01$, Shapiro–Wilk test), the median and interquartile range would be calculated for each treatment group and median differences and Hodges–Lehmann 2-tailed 95% confidence interval would be calculated for each comparison between AMR101 and placebo.

Nonparametric analysis p values were planned using Wilcoxon rank-sum test for each comparison between AMR101 and placebo. Missing data were imputed using the last-observation-carried-forward method. To control the family-wise error rate when performing multiple pairwise tests between the 2 dose levels of AMR101 and placebo, a prespecified step-down testing procedure was followed for the primary end point: differences in TG-lowering between AMR101 4 g/day and placebo were tested; if this first comparison showed a statistically significantly greater decrease in TG at the prespecified significance level of 0.05, the TG-lowering effects of AMR101 2 g/day versus placebo were also analyzed. For all end points, comparisons between AMR101 and placebo were made using a significance level of 0.05. The Hommel procedure was used to test the adequate control of type 1 error for multiple secondary end points. For non-HDL cholesterol, VLDL cholesterol, lipoprotein-associated phospholipase A_2, and apolipoprotein B, treatment groups were compared using the Dunnett test to control the type I error rate within each parameter. Changes in TG and non-HDL cholesterol were analyzed by select baseline characteristics in prespecified (TG) and post hoc (non-HDL cholesterol) analyses. All safety analyses were

Table 1
Baseline characteristics

Characteristic	AMR101 Dose		Placebo (n = 233)
	4 g/day (n = 233)	2 g/day (n = 236)	
Age (years), mean ± SD	61.1 ± 10.03	61.8 ± 9.42	61.2 ± 10.05
Age ≥65 years	91 (39%)	95 (40%)	87 (37%)
Men	142 (61%)	144 (61%)	145 (62%)
White	226 (97%)	226 (96%)	224 (96%)
Weight (kg), mean ± SD	94.5 ± 18.30	95.5 ± 18.29	97.0 ± 19.14
Body mass index (kg/m^2), mean ± SD	32.7 ± 4.99	32.9 ± 4.98	33.0 ± 5.04
Diabetes mellitus	171 (73%)	172 (73%)	171 (73%)
Fasting plasma glucose (mg/dl), mean ± SD (n = 225, 234, 227)	133.0 ± 37.1	135.4 ± 43.2	130.1 ± 35.8
Hemoglobin A1c (%), mean ± SD (n = 226, 234, 227)	6.6 ± 0.9	6.7 ± 1.1	6.5 ± 0.9
Statin use			
Atorvastatin	44 (19%)	43 (18%)	45 (19%)
Simvastatin	134 (58%)	136 (58%)	133 (57%)
Rosuvastatin	55 (24%)	57 (24%)	55 (24%)
Statin efficacy regimens*			
Lower	16 (7%)	17 (7%)	15 (6%)
Medium	148 (64%)	148 (63%)	144 (62%)
Higher	69 (30%)	71 (30%)	74 (32%)

Data are reported for the randomized population, with the exception of fasting plasma glucose and hemoglobin A1c, which are reported for the intent-to-treat population.

* Lower-efficacy statin regimens = simvastatin 5 to 10 mg; medium-efficacy statin regimens = rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; higher-efficacy statin regimens = rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg.

performed in the safety population (randomized patients who received ≥1 dose of study medication). For hemoglobin A1c and fasting plasma glucose, differences in change from baseline between AMR101 and placebo were analyzed using an analysis of covariance model with treatment as a factor and baseline value as a covariate using a significance level of 0.05.

Results

Figure 2 shows the patient disposition; 663 patients (>90% in each treatment group) completed the 12-week double-blinded treatment phase. Baseline characteristics of randomized patients are listed in Table 1 and were comparable across treatment groups ($p > 0.14$ for all comparisons; not presented in Table 1). Patients with diabetes had well-controlled diabetes with mean baseline hemoglobin A1c <7% and fasting plasma glucose <136 mg/dl for all groups. Median LDL cholesterol level was 83.0 mg/dl and 21% of patients had baseline LDL cholesterol levels <70 mg/dl. Most patients (93.2%) were taking medium- or high-efficacy statin regimens (as defined a priori) and 90.2% were on statin therapy before screening. Median baseline TG level was 259.0 mg/dl.

AMR101 produced significant decreases in TG and various efficacy end points in placebo-adjusted changes from baseline to study end (Figure 3 and Table 2). Because a significant departure from normality was observed for all efficacy end points ($p < 0.01$, Shapiro–Wilk test), nonparametric statistics were used. For the 2 AMR101 treatment groups, the maximum TG-lowering effect was reached by approximately week 4 (data not shown). AMR101 did not significantly increase LDL cholesterol at either dose. The noninferiority criterion for LDL cholesterol was met for the 2 AMR101 doses because the prespecified upper boundary of the 97.5% confidence interval (−1.7 to +0.5 for AMR101 4 and 2 g/day, respectively) did not cross the +6% noninferiority threshold (data not shown).

Analysis of subgroups by prespecified statin efficacy regimen indicated that patients treated with more effective statin regimens exhibited greater TG and non-HDL cholesterol decreases with AMR101 compared to lower-efficacy regimens (Table 3). Statistically significant decreases in TG levels with AMR101 4 g/day were observed for patients treated with atorvastatin, simvastatin, and rosuvastatin and with AMR101 2 g/day for patients treated with simvastatin. Analysis of subgroups by median baseline TG tertiles indicated that higher baseline TG levels resulted in greater TG decreases. Median decreases in TG levels were statistically significant versus placebo and similar in patients with and without diabetes mellitus.

During the double-blinded treatment period, 46.2% of patients had ≥1 treatment-emergent adverse event regardless of cause: 106 patients (45.5%) in the AMR101 4 g/day group, 106 patients (44.9%) in the AMR101 2 g/day group, and 112 patients (48.1%) in the placebo group. Most treatment-emergent adverse events were mild or moderate in severity and considered unrelated to study drug. Diarrhea, nausea, nasopharyngitis, and arthralgia occurred in >3% of patients, and only arthralgia occurred in a larger percentage of patients treated with AMR101 versus placebo (Table 4). The most common treatment-emergent adverse events were gastrointestinal disorders, which occurred in a larger percentage of patients in the placebo group. Eructations were reported by 2, 1, and 4 patients receiving AMR101 4 g/day, AMR101 2 g/day, and placebo, respectively. Twenty-five patients (3.6%) discontinued treatment during the double-blinded treatment phase because of a treatment-emergent adverse event (5 patients in AMR101 4 g/day group, 8 patients in AMR101 2 g/day group, and 12 patients in placebo group). In total, 18 serious adverse events were reported during the study (7 patients in AMR101 4 g/day group, 6 patients in AMR101 2 g/day group, and 5 patients in placebo group including 1 death related to myocardial infarction). No serious adverse events were considered related to study drug. No clinically significant increases in alanine aminotransferase, aspartate aminotransferase, and creatine kinase were observed in the AMR101 treatment groups. One patient in the AMR101 4 g/day group had an increase in alanine aminotransferase >3 times the upper limit of normal detected at week 12, which decreased during follow-up after the study. No statistically significant increases in fasting plasma glucose or hemoglobin A1c were observed in either treatment group compared to placebo. No clinically meaningful changes in safety laboratory parame-

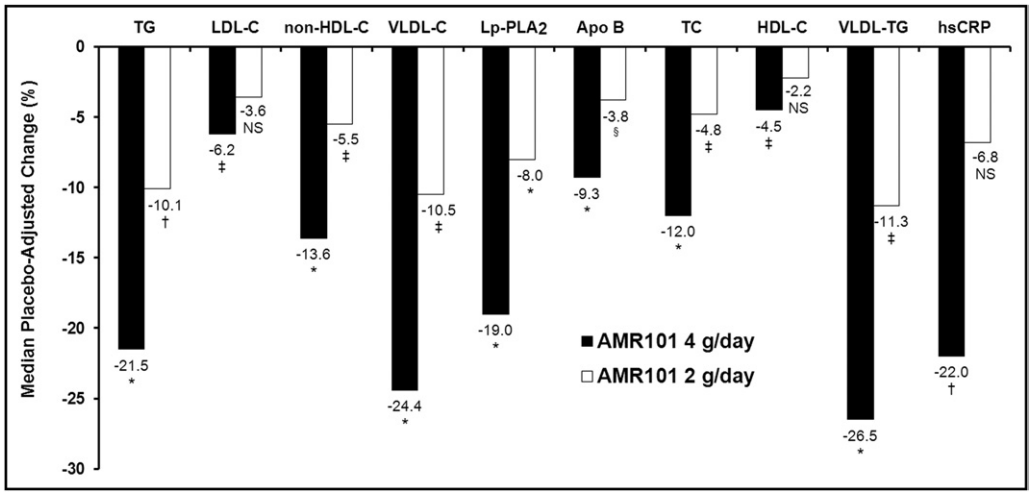

Figure 3. Median placebo-adjusted percent change from baseline to week 12 for efficacy end points (intent-to-treat population). *p <0.0001; †p <0.001; ‡p <0.01; §p <0.05. apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; NS = not significant; TC = total cholesterol; TG = triglyceride; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.

ters, electrocardiographic parameters, vital signs, or physical examination findings were noted.

Discussion

In this randomized trial of statin-treated patients at high risk of coronary artery disease with optimized LDL cholesterol levels and residually elevated TG levels, AMR101 4 and 2 g/day significantly decreased median placebo-adjusted TG levels from baseline by 21.5% and 10.1%, respectively. Although LDL cholesterol levels were well controlled at baseline and most patients were taking medium- or high-efficacy statin regimens (93.2%), AMR101 4 g/day significantly decreased median placebo-adjusted LDL cholesterol levels by an additional 6.2%. Furthermore, AMR101 decreased non-HDL cholesterol (13.6%) and apolipoprotein B (9.3%). Patients treated with more effective statin regimens showed greater decreases in TG and non-HDL cholesterol with AMR101 4 g/day compared to less-effective regimens. AMR101 decreased TG levels similarly in patients regardless of diabetes mellitus status or statin type, with the greatest TG decreases seen in higher-tertile baseline TG (31% in 4 g/day group compared to placebo). Based on this study, AMR101 4 g/day appears to be a more effective dose than 2 g/day because changes in efficacy end points were greater with the higher dose.

One of the potential explanations for the continued increase of cardiovascular risk in high-risk patients with persistent high TG elevations despite statin therapy may be due to increased inflammation. AMR101 4 g/day decreased median placebo-adjusted lipoprotein-associated phospholipase A$_2$ by 19% and decreased high-sensitivity C-reactive protein by 22.0%.

Although other studies in hypertriglyceridemic patients on statin therapy have suggested EPA and docosahexaenoic acid (DHA) combinations may decrease non-HDL cholesterol,[5,6] lipoprotein-associated phospholipase A$_2$,[7] and possibly apolipoprotein B,[5] AMR101 not only decreased these parameters but also decreased LDL cholesterol and high-sensitivity C-reactive protein levels. Decreases in non-HDL cholesterol, lipoprotein-associated phospholipase A$_2$, and apolipoprotein B in the present study were greater than expected. In the Combination of Prescription Omega-3 with Simvastatin (COMBOS) study,[5] which enrolled patients without regard to coronary heart disease risk on stable simvastatin therapy and with similarly elevated TGs, 4 g/day of a prescription ω-3 combination EPA and DHA ethyl ester formulation decreased median TG levels by 29.5% versus 6.3% with placebo (p <0.001). Omega-3 acid ethyl esters combined with simvastatin significantly decreased the primary end point of median change in non-HDL cholesterol (9.0% vs 2.2%; p <0.001) and median change in apolipoprotein B (4.2% vs 1.9%; p = 0.023) compared to simvastatin alone. In this trial, the combined EPA and DHA prescription preparation resulted in a nonsignificant increase in LDL cholesterol levels of 0.7%, compared to a 2.8% decrease in patients treated with placebo (p = 0.052).

The LDL cholesterol effect seen in the present trial with AMR101 is supported by the Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week Study with an Open-label Extension (MARINE),[4] which enrolled patients with very high TGs (≥500 and ≤2,000 mg/dl). In the MARINE study, AMR101 significantly decreased TG levels but did not increase LDL cholesterol compared to placebo. This contrasts with the effect on LDL cholesterol with combination EPA and DHA preparations wherein administration to patients with very high TG levels increased LDL cholesterol as much as 49% compared to placebo.[8] Definitive differences between EPA and EPA plus DHA await head-to-head clinical trials. However, a previous double-blinded, randomized, parallel-design controlled trial in 121 healthy men and women showed that the DHA group had significant increases in LDL cholesterol, whereas the pure EPA group had significant decreases in small dense LDL cholesterol and lipoprotein-associated phospholipase A$_2$.

Table 2
Changes in efficacy end points from baseline to week 12 (intent-to-treat population)

Variable	AMR101 Dose						Placebo (n = 227)			Median Placebo-Adjusted Change From Baseline			
	4 g/day (n = 226)			2 g/day (n = 234)			Baseline	End of Treatment	Change From Baseline (%)	AMR101 4 g/day vs Placebo (%)	p Value	AMR101 2 g/day vs Placebo (%)	p Value
	Baseline	End of Treatment	Change From Baseline (%)	Baseline	End of Treatment	Change From Baseline (%)							
Primary end point													
Triglycerides (mg/dl) (n = 226, 234, 227)	264.8 (93.0)	220.8 (92.0)	−17.5 (31.0)	254.0 (92.5)	244.3 (117.0)	−5.6 (34.5)	259.0 (81.0)	269.5 (149.5)	5.9 (44.9)	−21.5	<0.0001	−10.1	0.0005
Secondary end points													
Low-density lipoprotein cholesterol (mg/dl) (n = 225, 233, 226)	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	82.0 (24.0)	87.0 (27.0)	2.4 (26.1)	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	−6.2	0.0067	−3.6	0.0867
Non-high-density lipoprotein cholesterol (mg/dl) (n = 226, 234, 227)	128.0 (32.0)	122.0 (39.0)	−5.0 (21.3)	128.0 (33.0)	134.0 (41.0)	2.4 (26.1)	128.0 (34.0)	138.0 (43.0)	9.8 (27.6)	−13.6	<0.0001	−5.5	0.0054
Very-low-density lipoprotein cholesterol (mg/dl) (n = 225, 233, 226)	44.0 (21.0)	38.0 (22.0)	−12.1 (47.9)	43.0 (21.0)	44.0 (25.0)	1.6 (54.6)	42.0 (21.0)	49.0 (28.0)	15.0 (58.8)	−24.4	<0.0001	−10.5	0.0093
Lipoprotein-associated phospholipase A_2 (ng/ml) (n = 217, 224, 213)	180.0 (56.0)	160.0 (57.0)	−12.8 (18.5)	190.0 (55.5)	183.5 (57.5)	−1.8 (23.1)	185.0 (58.0)	200.0 (71.0)	6.7 (24.0)	−19.0	<0.0001	−8.0	<0.0001
Apolipoprotein B (mg/dl) (n = 217, 227, 219)	93.0 (23.0)	90.0 (25.0)	−2.2 (16.4)	91.0 (22.0)	95.0 (24.0)	1.6 (20.7)	91.0 (24.0)	98.0 (25.0)	7.1 (23.2)	−9.3	<0.0001	−3.8	0.0170
Selected exploratory end points													
Total cholesterol (mg/dl) (n = 226, 234, 227)	167.0 (38.0)	162.0 (38.0)	−3.2 (16.8)	169.0 (34.0)	175.0 (44.0)	2.1 (19.6)	168.0 (38.0)	181.0 (46.0)	9.1 (20.8)	−12.0	<0.0001	−4.8	0.0019
High-density lipoprotein cholesterol (mg/dl) (n = 226, 234, 227)	37.0 (12.0)	37.0 (13.0)	−1.0 (18.2)	38.0 (13.0)	38.0 (11.0)	0.0 (19.5)	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	−4.5	0.0013	−2.2	0.1265
Very-low-density lipoprotein triglycerides (mg/dl) (n = 225, 233, 226)	190.0 (99.0)	147.0 (88.0)	−19.2 (46.2)	185.0 (86.0)	168.0 (98.0)	−2.1 (48.9)	183.0 (94.0)	196.0 (136.0)	8.9 (63.8)	−26.5	<0.0001	−11.3	0.0049
High-sensitivity C-reactive protein (mg/l) (n = 217, 227, 219)	2.2 (2.7)	2.0 (3.0)	−2.4 (62.8)	1.9 (2.9)	2.5 (3.4)	10.3 (88.6)	2.2 (4.0)	2.6 (4.7)	17.1 (108.0)	−22.0	0.0005	−6.8	0.2889

Data are presented as median (interquartile range) for end point values.

Table 3
Changes in triglyceride and non-high-density lipoprotein cholesterol end points from baseline to week 12 (intent-to-treat population subgroups)

Variable	AMR101 Dose						Placebo (n = 227)			Median Placebo-Adjusted Change			
	4 g/day (n = 226)			2 g/day (n = 234)			Baseline	End of Treatment	Change From Baseline (%)	AMR101 4 g/day vs Placebo (%)	p Value	AMR101 2 g/day vs Placebo (%)	p Value
	Baseline	End of Treatment	Change From Baseline (%)	Baseline	End of Treatment	Change From Baseline (%)							
Changes in triglyceride value by statin efficacy regimen*													
Lower (n = 16, 15, 14)	267.8 (87.0)	256.8 (131.5)	0.5 (38.2)	256.0 (64.0)	208.5 (162.0)	−18.8 (46.3)	315.0 (148.5)	304.5 (158.5)	19.4 (61.0)	−13.1	0.5467	−13.8	0.6784
Medium (n = 141, 148, 140)	269.0 (96.5)	221.0 (91.0)	−15.8 (30.3)	253.8 (83.0)	248.0 (116.0)	−5.3 (34.0)	257.3 (83.5)	268.3 (131.3)	4.6 (44.4)	−20.1	<0.0001	−8.7	0.0139
High (n = 69, 71, 73)	254.5 (92.5)	214.5 (87.0)	−20.2 (20.8)	256.5 (103.5)	239.5 (115.0)	−5.8 (31.2)	257.5 (76.5)	266.0 (160.0)	6.5 (45.0)	−26.0	<0.0001	−11.7	0.0200
Changes in non-high-density lipoprotein cholesterol value by statin efficacy regimen*†													
Lower (n = 16, 15, 14)	128.0 (24.0)	131.0 (36.5)	−1.4 (29.3)	139.0 (20.0)	135.0 (28.0)	−2.2 (28.7)	149.5 (50.0)	152.0 (45.0)	1.5 (31.1)	2.4	0.6326	3.3	0.7107
Medium (n = 141, 148, 140)	129.0 (35.0)	124.0 (40.0)	−4.3 (24.2)	126.5 (35.5)	133.0 (40.0)	1.7 (23.5)	128.0 (35.0)	139.5 (42.5)	10.5 (25.1)	−13.9	<0.0001	−7.1	0.0031
High (n = 69, 71, 73)	128.0 (31.0)	118.0 (38.0)	−6.3 (19.9)	128.0 (31.0)	142.0 (47.0)	5.4 (28.4)	126.0 (27.0)	134.0 (41.0)	12.3 (28.6)	−15.8	<0.0001	−3.5	0.3266
Changes in triglyceride value by statin type													
Atorvastatin (n = 41, 43, 45)	281.5 (59.0)	216.0 (82.5)	−23.9 (18.6)	235.0 (89.0)	245.0 (125.0)	−0.5 (34.0)	247.0 (71.0)	266.0 (142.5)	7.8 (44.6)	−28.4	<0.0001	−2.4	0.6642
Simvastatin (n = 131, 134, 128)	262.0 (106.0)	228.0 (114.5)	−14.7 (31.8)	256.5 (102.0)	241.3 (133.0)	−8.8 (33.2)	262.0 (97.8)	274.5 (148.3)	6.0 (43.2)	−18.8	<0.0001	−14.3	0.0004
Rosuvastatin (n = 54, 57, 54)	250.8 (85.5)	204.0 (77.0)	−20.5 (39.1)	258.0 (93.5)	252.5 (99.0)	−5.8 (30.8)	258.3 (69.0)	268.3 (147.0)	−0.6 (46.2)	−23.4	<0.0001	−5.7	0.2512
Changes in triglyceride value by diabetes status													
Diabetes (n = 165, 171, 165)	262.0 (92.0)	216.5 (88.0)	−18.7 (31.9)	253.5 (87.0)	244.0 (116.5)	−1.5 (36.9)	259.0 (78.0)	275.5 (153.5)	6.2 (43.4)	−23.2	<0.0001	−9.8	0.0074
No diabetes (n = 61, 63, 62)	271.5 (114.5)	234.5 (90.0)	−15.0 (29.1)	256.5 (96.0)	245.0 (121.5)	−12.1 (24.7)	258.8 (123.5)	258.5 (138.0)	4.3 (43.0)	−16.8	0.0005	−10.8	0.0261
Changes in triglyceride value by baseline triglyceride tertile‡													
First tertile (n = 68, 84, 72)	207.8 (28.0)	183.5 (67.5)	−10.9 (33.5)	205.8 (33.0)	207.8 (74.5)	0.7 (36.4)	203.8 (31.5)	214.5 (71.5)	7.9 (36.4)	−14.4	0.0020	−4.1	0.3694
Second tertile (n = 81, 76, 80)	261.5 (26.0)	205.0 (74.5)	−19.3 (32.0)	257.0 (30.5)	228.3 (83.5)	−13.0 (30.7)	257.8 (30.3)	263.5 (112.3)	3.3 (39.7)	−17.9	<0.0001	−9.9	0.0324
Third tertile (n = 77, 74, 75)	346.5 (75.5)	260.0 (110.5)	−21.8 (25.9)	348.5 (75.0)	320.3 (119.0)	−8.7 (35.4)	340.5 (94.0)	380.5 (165.5)	5.2 (56.2)	−31.1	<0.0001	−16.9	0.0043

Data are presented as median (interquartile range) for end point values; triglyceride and non-high-density lipoprotein values are milligrams per deciliter.

* Lower-efficacy statin regimens = simvastatin 5 to 10 mg; medium-efficacy statin regimens = rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; higher-efficacy statin regimens = rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg.

† Post hoc analysis.

‡ First tertile <230.5 mg/dl; second tertile 230.5 to <289.5 mg/dl; third tertile ≥289.5 mg/dl.

Table 4
Treatment-emergent adverse events* occurring in more than three percent of patients (safety population)

System Organ Class, Preferred Term	AMR101 Dose		Placebo (n = 233)	Total (n = 702)
	4 g/day (n = 233)	2 g/day (n = 236)		
Gastrointestinal disorders				
All	27 (11.6%)	27 (11.4%)	40 (17.2%)	94 (13.4%)
Diarrhea	8 (3.4%)	9 (3.8%)	10 (4.3%)	27 (3.8%)
Nausea	5 (2.1%)	5 (2.1%)	7 (3.0%)	17 (2.4%)
Infections and infestations				
All	31 (13.3%)	30 (12.7%)	38 (16.3%)	99 (14.1%)
Nasopharyngitis	1 (0.4%)	6 (2.5%)	7 (3.0%)	14 (2.0%)
Musculoskeletal and connective tissue disorders				
All	18 (7.7%)	18 (7.6%)	10 (4.3%)	46 (6.6%)
Arthralgia	4 (1.7%)	8 (3.4%)	1 (0.4%)	13 (1.9%)

* Treatment-emergent adverse events were defined as any adverse event that began after the first dose of double-blinded study drug or occurred before the first dose and worsened in severity during the double-blinded treatment period.

The investigators postulated that other beneficial effects of EPA include decreases in lipoprotein-associated phospholipase A_2, fibrinogen, small dense LDL cholesterol, and TG-rich lipoprotein cholesterol content and increases in very small precursor pre-β1 migrating HDL.[9]

In this study, AMR101 was safe and generally well tolerated at the 2 doses; of the treatment-emergent adverse events reported by >3% of patients in any group, only incidence of arthralgia was increased compared to placebo, but this was neither dose dependent nor observed in the MARINE study.[4] No clinically significant effects were reported with regard to liver or kidney evaluations as evidenced by alanine aminotransferase, aspartate aminotransferase, and creatine kinase. Because EPA and DHA preparations are sometimes reported to (transiently) increase glucose levels,[5] it is perhaps relevant to note that AMR101 had no significant effects on glucose metabolism as evidenced by no change in fasting plasma glucose and hemoglobin A1c, which is especially important in patients with diabetes mellitus, who constitute a large population of patients with mixed dyslipidemia.

A limitation of the present study is that the investigation examined the efficacy of 2 doses of AMR101 versus placebo and not in comparison to currently available therapies. Also, although a protocol amendment expanded the lipid entry criteria, this would not be expected to affect interpretation of study results. There also remains a need for outcomes data to determine whether the lipid and other biomarker changes seen with AMR101 translate into a decrease in cardiovascular events. Recent clinical trials have failed to show decreases in cardiovascular events with fenofibrate (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD]; Action to Control Cardiovascular Risk in Diabetes-Lipid [ACCORD-Lipid]) with and without statin therapy[10,11] or with niacin in combination with statin therapy (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health [AIM-HIGH]).[12] Previous ω-3 fatty acid trials[13] have tended to support recommendations made by organizations such as the American Heart Association, wherein 1 g of ω-3 fatty acid therapy is recommended for patients with cardiovascular disease,[14] although definitive trials are needed, and 2 to 4 g of ω-3 fatty acids are recommended to lower TG levels.[3] Furthermore, the Japan EPA Lipid Intervention Study (JELIS) demonstrated a significant decrease in the 5-year cumulative rate of major coronary events (19%, p = 0.011) in Japanese patients treated with highly purified EPA (1.8 g/day) on statin therapy.[15] To obtain outcome data, a cardiovascular outcomes study with AMR101 4 g/day, the Reduction of Cardiovascular Events with EPA—Intervention Trial (REDUCE-IT; NCT01492361), is currently recruiting patients and is planned in approximately 8,000 patients at high risk for cardiovascular events.

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Appendix

ANCHOR study investigators: Christie Ballantyne, MD (primary investigator), Leslie Barkis, DO, Harold Bays, MD, Richard Beasley, MD, Jolene Berg, MD, Bruce Bowling, MD, Cristian Francisco Breton, MD, George Canas, MD, Albert Carr, MD, David Catlett, MD, Mark Cervi, MD, Walter Chi, MD, Steven Chrysant, MD, Kenneth Cohen, MD, Milissa Cooper, DO, Steven Cox, DO, H. Jackson Downey, MD, John Earl, MD, Brian Feaver, MD, Neil Fraser, MD, Raul Gaona, Sr., MD, Richard Glover, MD, C. Allen Goetsch, MD, Anne Goldberg, MD, John Guyton, MD, Terence Hart, MD, Charles Herring, MD, John Homan, MD, Randall Huling, Jr., MD, Richard Hyman, MD, Terence Isakov, MD, John Jackson, MD, Timothy Jackson, MD, William Kaye, MD, Dean Kereiakes, MD, Boris Kerzner, MD, Andrew Kim, MD, Eric Klein, MD, Stanley Koch, MD, Timothy Koehler, DO, Pam Laubscher, DO, Andrea Lawless, MD, Denny Lee, MD, Lawrence Levinson, MD, Andrew Lewin, MD, Robert Lipetz, DO, Richard Lorraine, MD, Barry Lubin, MD, Marissa Magsino, MD, Sashi Makam, MD, Richard Marple, MD, Gilbert Martinez, MD, Mary McGowan, MD, James McKenney, PharmD, Roger Miller, MD, Richard Mills, MD, Patrick Moriarty, MD, Abel Murillo, MD, Steven Nash, MD, Stephen Ong, MD, Naynesh Patel, MD, Rajesh Patel, MD, Sanford Plevin, MD, Edward Portnoy, MD, John Pullman, MD, James Quigley, MD, Alan Reichman, MD, James Rhyne, MD, Dennis Riff, MD, Scott Rigby, MD, Jeffrey Rosen, MD, Julio Rosenstock, MD, Eli Roth, MD, John Rubino, MD, Jaime Sandoval, MD, Anthony John Scarsella, MD, Larry Seidman, DO, Michael Seidner, MD, John Sensenbrenner, MD, Loknath Shandilya, MD, Richard Shultzaberger, MD, Teresa Sligh, MD, Diane Smith, MD, Evan Stein, MD, Craig S. Thompson, MD, Gregory Thomas, MD, Phillip Toth, MD, Miguel Trevino, MD, Daniel Weiss, MD, Robert Weiss, MD, Alexander White, MD, James Wigand, MD, and Jonathan Wilson, DO.

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